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Differences in the risk of clinical failure between thiopurine and methotrexate in bio-naïve patients with Crohn's disease: a Korean nationwide population-based study

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Abstract

Background: Although immunomodulators are widely prescribed in patients with Crohn's disease (CD), it is unclear whether there is a difference in treatment outcomes between thiopurines and methotrexate (MTX).

Objective: To compare the risk of clinical failure between thiopurines and MTX in bio-naïve patients with CD.

Design: Nationwide, population-based study.

Methods: We used claims data from the Korean National Health Insurance Service. After inverse probability of treatment weighting, logistic regression and Cox proportional hazard analyses were used to evaluate the risk of clinical failure in bio-naïve patients with CD treated with thiopurine (thiopurine group) or MTX (MTX group).

Results: Overall, 10,296 adult and pediatric patients with CD [9912 (96.3%) and 384 (3.7%) in the thiopurine and MTX groups, respectively] were included. The odds ratios (ORs) of failure to induce remission were significantly higher in the MTX group than in the thiopurine group [adjusted OR (aOR), 1.115; 95% confidence interval (CI), 1.045–1.190; $p = 0.001$]. However, the opposite result was observed only in patients without concomitant steroid use: the MTX group had a lower risk of induction failure than the thiopurine group (aOR, 0.740; 95% CI, 0.673–0.813; $p < 0.001$). The risk of overall maintenance failure was higher in the MTX group than in the thiopurine group [adjusted hazard ratio (aHR), 1.117; 95% CI, 1.047–1.191; $p = 0.001$]. The risk of overall maintenance failure was higher in the standard-dose MTX group than in the low-dose MTX group (aHR, 1.296; 95% CI, 1.134–1.480; $p < 0.001$). There was no significant difference in the risk of maintenance failure according to the administration route of MTX.

Conclusion: Thiopurine is more effective than MTX in inducing and maintaining remission in bio-naïve patients with CD; however, the concomitant use of steroids influences inducing remission.

Plain language summary

Differences in treatment efficacy between thiopurine and methotrexate in patients with Crohn's disease who were not treated with biologics

Immunomodulators (IMMs) used in the treatment of Crohn's disease (CD) include medications such as thiopurine and methotrexate (MTX). Although IMMs are widely prescribed for patients with CD, it remains unclear whether treatment outcomes differ according to the specific types and dosages of IMMs and administration routes of MTX. In this study, we investigated the risk of treatment failure between thiopurines and MTX in CD patients not undergoing biologic treatment. Patients treated with MTX had a higher

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risk of maintenance failure than those treated with thiopurines. There was no difference in the risk of treatment failure according to the dosage of thiopurine. However, the risk of maintenance failure was higher in patients receiving standard-dose MTX than in those receiving low-dose MTX. There was no difference in the risk of maintenance failure according to the administration route of MTX. Our study enriches the knowledge regarding the treatment efficacy of thiopurines and MTX for patients with CD and may help clinicians develop appropriate treatment plans.

Keywords: Crohn's disease, methotrexate, thiopurine

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Introduction

Immunomodulators (IMMs) include antimetabolites of purines and pyrimidines, such as thiopurines (azathioprine and 6-mercaptopurine) and methotrexate (MTX). Although IMMs have been prescribed for Crohn's disease (CD) for more than 50 years, their treatment efficacy has not been well evaluated, and adverse events and loss of response can be barriers to IMM treatment. Thiopurine monotherapy is beneficial for reducing the risk of surgery and sustaining steroid-free remission in patients with CD[1]; in addition, combination therapy using thiopurine and antitumor necrosis factor (TNF) agents shows a better outcome than anti-TNF monotherapy.[2] Although MTX is also effective for the induction and maintenance of remission in patients with CD,[3,4] most studies on MTX evaluated its treatment efficacy and safety in patients who had already failed thiopurine therapy.[5,6] There is little information regarding the efficacy of MTX in patients with CD who are naïve to thiopurines. Moreover, most previous studies on the treatment efficacy of MTX in patients with CD lacked information regarding patient history of biologics or did not distinguish between bio-naïve and bio-experienced patients.[7] Therefore, our study aimed to compare the risk of clinical failure in bio-naïve patients with CD treated with either thiopurines or MTX using Korean nationwide population data.

Materials and methods

Data source and definitions

The study population was derived from claims data in the Korean National Health Insurance Service (NHIS) database between July 2007 and December 2021. The Korean NHIS is obligatory for most Koreans and covers approximately 97% of the population.[8] Therefore, the medical information of almost all Korean patients is available in the Korean NHIS claims database, which includes information on demographics, diagnoses, hospital admissions, emergency room (ER) visits, medical treatments, and operations.

Diagnostic information was obtained using the International Classification of Diseases 10th Revision (ICD-10) codes. Information regarding medical prescriptions and operations was also retrieved. The type of medications prescribed for CD included steroids (hydrocortisone, prednisolone, and methylprednisolone), thiopurines (azathioprine and 6-mercaptopurine), MTX, anti-TNF agents (adalimumab and infliximab), ustekinumab, and vedolizumab. Previous exposure to steroids was defined as a steroid prescription from 365 to 91 days before the initiation of IMMs after the diagnosis of CD. The concomitant use of steroids was defined as a steroid prescription from 90 days before to 14 days after the initiation of IMMs. Inflammatory bowel disease (IBD)-related operations were classified as bowel resection or perianal surgery. Bowel resection included operations that removed all or some parts of the small intestine or colon, whereas perianal surgery included fistulectomy, fistulotomy, seton operation, and operations for perianal abscesses.

Study design

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (IRB No. X-2202-741-902). Study findings were reported in

accordance with the STROBE guidelines for reporting observational studies[9] (Supplemental Note). Patients diagnosed with CD were identified based on the presence of the respective ICD-10 code (K50) during inpatient or outpatient medical care between July 2009 and December 2019. If IMMs were prescribed prior to the first imposition of the K50 code and there was less than a 90-day difference between the first prescription of the IMMs and the first imposition of the code, it was considered that CD was diagnosed on the day when IMMs were initiated. The thiopurine group included patients who were prescribed azathioprine or 6-mercaptopurine, and the MTX group included those who were prescribed MTX. A prescription period should be more than 1 consecutive week. Because the clinical response for thiopurine or MTX was expected 3–4 months after starting thiopurine or MTX,[10] patients whose prescription period was longer than 112 days were included in our analysis.

The exclusion criteria were as follows: (1) patients who were prescribed thiopurines and MTX simultaneously; (2) patients in whom biologics were initiated before IMM treatment; and (3) those diagnosed with rheumatoid diseases, psoriasis, IgG4-related diseases, or cancer before the diagnosis of CD. The final criterion was included to rule out the possibility of an IMM prescription for diseases other than CD. We identified the diagnoses of rheumatoid diseases, psoriasis, and IgG4-related diseases using their respective ICD-10 codes (rheumatoid diseases, M08, M09, M30, M31, M32, M33, M34, M35, M45; psoriasis, L40; IgG4-related diseases, D898). Cancer, for which IMMs may be prescribed, was identified using ICD-10 code C. The diagnostic codes for rare diseases and cancers are thoroughly monitored by the NHIS to ensure accurate diagnosis and that proper insurance benefits are provided to patients with rare diseases or cancers.[11] All patients meeting the inclusion criteria and not meeting the exclusion criteria in the claims data from the Korean NHIS were included in the analyses. However, our study excluded patients aged <5 years because it was difficult to obtain appropriate medical data from the NHIS database for these patients.

Study outcomes

The primary outcome was the risk of clinical failure in the MTX group compared with that in the thiopurine group. The index date was defined as the date of the first IMM prescription. Clinical failure within 112 days of the index date was considered an induction failure.[12] Thiopurine may take 3–4 months to show clinical efficacy, and the Korean NHI system requires previous IMM treatment failure for the insurance to cover biologics or small molecules. Although thiopurine monotherapy was ineffective for induction therapy,[13] the combination treatment of systemic steroids and thiopurine for induction treatment is reasonable in Korea.[14] Therefore, induction failure was compared between the MTX and thiopurine groups. The maintenance period began 112 days after the index date, and we evaluated the risk of maintenance failure for 1 year and the overall period between the MTX and thiopurine groups.

Systemic steroid prescription, IMM switching, biologics initiation, and CD-related operations were considered clinical failures. During the induction period, failure to discontinue steroid treatment within 112 days of the index date was also considered a clinical failure in patients who were using steroids at the time of IMM initiation. Because health insurance coverage of biologics in Korea is limited to patients who have experienced treatment refractoriness or IMM-related adverse events,[15] biologics initiation can be regarded as IMM treatment failure in Korea. We also compared the risk of persistence failure between the thiopurine and MTX groups. Patients were eligible for this analysis when they continued the IMM treatment for more than 16 weeks from the index date.[16,17] Persistence failure refers to discontinuing MTX or thiopurine for more than 60 days, irrespective of the underlying cause. Like maintenance failure, we evaluated the risk of persistence failure for 1 year and the overall period between the MTX and thiopurine groups.

Subgroup analyses compared differences in clinical failure according to the doses of IMMs and the administration route of MTX. Guidelines recommend azathioprine at doses of 2–2.5 mg/kg/day.[18] According to a study estimating the global population biomass based on reports from the World Health Organization, the sex-, age-, and region-adjusted average body weights of the global and Asian populations were 62.0 and 57.7 kg, respectively.[19] Because only a small number of Korean patients were prescribed high doses of azathioprine,[20] standard and low doses of

azathioprine were classified based on a dose of 60 mg/day in patients aged >12 years. Standard and low doses of 6-mercaptopurine were classified based on 30 mg/day because azathioprine is approximately 50% of 6-mercaptopurine by molecular weight.[21] The recommended doses of MTX were 25 and 15 mg/week for the induction and maintenance of remission, respectively.[22] A low dose of MTX was defined as <12.5 mg/week in patients aged >12 years.[23] The doses of IMMs in pediatric patients are smaller than those in adult patients because of the lower body weight of pediatric patients compared with that of adult patients. However, since individual body weight information was not available in the NHIS claims database, the body weight of pediatric patients (<13 years) was estimated according to their age (Supplemental Table 1).[24]

Statistical analysis

Statistical analyses were conducted by a professional statistician (EJ) using SAS Enterprise Guide version 7.15 (SAS Institute, Inc., Cary, NC, USA) and R version 3.5.1 (The R Foundation for Statistical Computing, Vienna, Austria). Continuous variables are presented as means ± standard deviation, and categorical variables as numbers and percentages (%). The standardized mean difference (SMD) was used to assess the differences in baseline covariates between the thiopurine and MTX groups. Inverse probability of treatment weighting (IPTW) was used to minimize the effect of confounding factors.[25] The following variables were used to calculate the propensity scores: age, sex, disease duration, CD-related operation, ER visit, previous steroid exposure, concomitant use of steroids, Charlson comorbidity index (CCI), and types of insurance.[26] The Korean public healthcare system provides two types of insurance: mandatory social health insurance and medical aid.[27] Since medical aid covers the lowest-income population in Korea, different types of insurance were included to adjust for the socioeconomic status of the population.

For group comparisons before and after IPTW, SMDs were calculated with a threshold of 0.2. Univariate analyses were performed using logistic regression to estimate the odds ratio (OR) with a 95% confidence interval (CI) for induction failure with respect to IMMs. A Cox proportional hazards model was used to analyze the time to clinical failure and persistence failure. The proportional hazard assumption was examined using the Grambsch and Therneau test based on Schoenfeld residuals.[28] When the proportional hazard assumption was violated, a time-dependent Cox proportional hazards model was used. In subgroup analyses, treatment failure depended on covariates with SMDs ⩾ 0.2 in each subgroup. Therefore, high SMD variables were adjusted to correct for potential bias and were considered reliable when the same trends were observed before and after the adjustment. A stratified Cox proportional hazard model was used when the proportional hazard assumption was violated for covariates with a high SMD. Statistical significance was set at $p < 0.05$. Other researchers can replicate our methodology by following the comprehensive description of the statistical analysis method.

Results

Baseline characteristics of the thiopurine and MTX groups

Among the 93,840 patients who had a diagnostic code of K50 between July 2007 and December 2019, those who were diagnosed with CD after July 2009 and prescribed IMMs for more than 7 days were identified, and those who were suspected to be undergoing IMM treatment for diseases other than CD were excluded (Figure 1). Finally, 10,296 patients with CD were included, of whom 9,912 were treated with thiopurines (96.3%) and 384 with MTX (3.7%). The age at diagnosis, sex, CD-related operation, ER visit, previous steroid exposure, concomitant use of steroids, CCI, and types of insurance were balanced between the two groups after IPTW (Supplemental Figure 1). After IPTW, approximately two-thirds of the patients were diagnosed with CD at the age of 17–39 years (thiopurine group, $n = 6{,}721.8$, 65.3%; MTX group, $n = 5{,}980.9$, 65.3%), and the number of men was greater than that of women (thiopurine group, $n = 7{,}583.6$, 73.7%; MTX group, $n = 6{,}754.0$, 73.7%) in the two groups (Table 1). The disease duration before the initiation of IMMs was longer in the MTX group than in the thiopurine group after IPTW (thiopurine group, 326.9 ± 605.0 days; MTX group, 636.7 ± 942.1 days; SMD = 0.391).

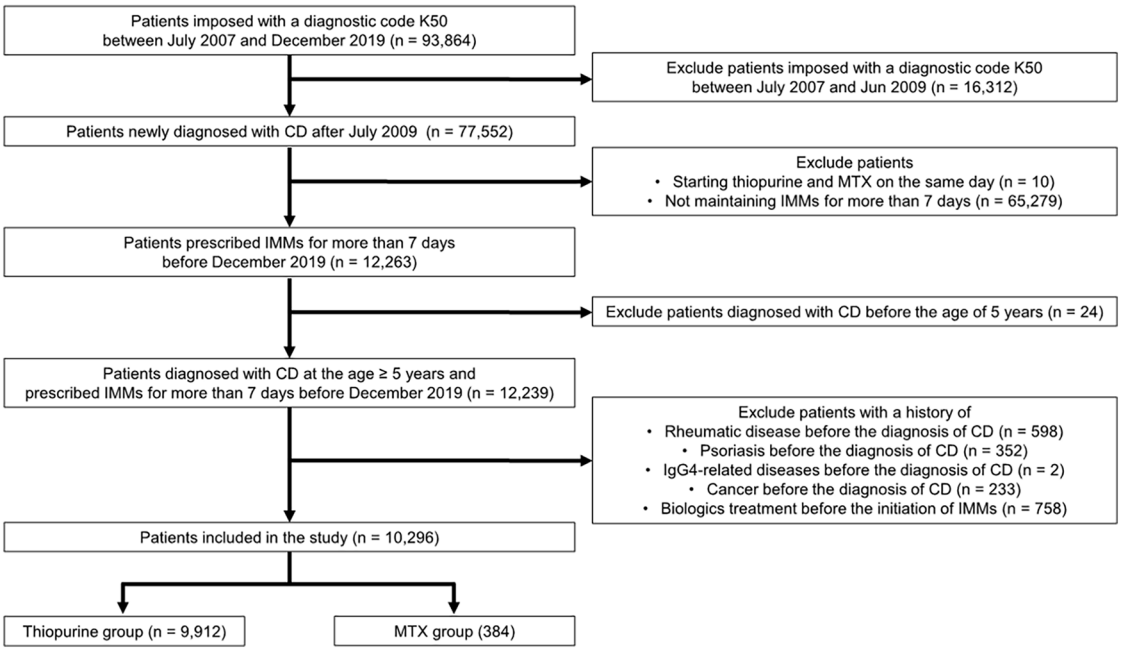

Figure 1. Flow diagram presenting the patient identification process.
CD, Crohn's disease; IMM, immunomodulator; MTX, methotrexate; *n*, number.

Table 1. Baseline characteristics of patients with Crohn's disease according to immunomodulators before and after the inverse probability of treatment weighting.

Characteristics	Before IPTW		SMD	After IPTW		SMD
	Thiopurine	MTX		Thiopurine	MTX	
N (%)	9,912 (96.3)	384 (3.7)		10,296.6 (52.9)	9,160.7 (47.1)	
Age at diagnosis, *n* (%)						
5–16	1,855 (18.7)	89 (23.2)	0.811	1,942.7 (18.9)	1,791.1 (19.6)	0.024
17–39	6,600 (66.6)	122 (31.8)		6,721.8 (65.3)	5,980.9 (65.3)	
⩾40	1,457 (14.7)	173 (45.1)		1,632.1 (15.9)	1,388.7 (15.2)	
Male, *n* (%)	7,368 (74.3)	216 (56.2)	0.387	7,583.6 (73.7)	6,754.0 (73.7)	0.002
Disease duration before the initiation of IMMs, day[a]	319.2 ± 591.3	764.1 ± 893.4	0.588	326.9 ± 605.0	636.7 ± 942.1	0.391
Bowel resection before the initiation of IMMs, *n* (%)	537 (5.4)	18 (4.7)	0.033	554.4 (5.4)	513.9 (5.6)	0.010
Perianal surgery before the initiation of IMMs, *n* (%)	562 (5.7)	6 (1.6)	0.221	568.1 (5.5)	373.2 (4.1)	0.068
ER visit within 1 year before the initiation of IMMs, *n* (%)	479 (4.8)	16 (4.2)	0.032	493.6 (4.8)	272.1 (3.0)	0.094
Previous steroid exposure, *n* (%)	2,421 (24.4)	62 (16.1)	0.207	2,481.9 (24.1)	2,212.6 (24.2)	0.001
Concomitant use of steroids, *n* (%)	4,011 (40.5)	77 (20.1)	0.456	4,088.5 (39.7)	3,466.3 (37.8)	0.038

(Continued)

Table 1. (Continued)

Characteristics	Before IPTW		SMD	After IPTW		SMD
	Thiopurine	MTX		Thiopurine	MTX	
Charlson comorbidity index, *n* (%)						
0	5,069 (51.1)	114 (29.7)	0.693	5,182.5 (50.3)	4,763.2 (52.0)	0.043
1	3,583 (36.1)	112 (29.2)		3,694.8 (35.9)	3,099.6 (33.8)	
⩾2	1,260 (12.7)	158 (41.1)		1,419.2 (13.8)	1,297.8 (14.2)	

[a]Data are presented as means ± standard deviations.
ER, emergency room; IMM, immunomodulator; IPTW, inverse probability of treatment weighting; MTX, methotrexate; *N*, number; SMD, standardized mean difference.

Comparison of the risk of clinical failure between the thiopurine and MTX group

The risk of induction failure was significantly higher in the MTX group than in the thiopurine group [adjusted OR (aOR) = 1.115; 95% CI = 1.045–1.190; $p = 0.001$], and 25.9% of the MTX group (adjusted $n = 2{,}375.6$) and 24.4% of the thiopurine group (adjusted $n = 2{,}507.9$) failed to induce clinical remission. The most common cause of induction failure was the initiation of biologics in both the thiopurine and MTX groups (thiopurine group, adjusted $n = 1{,}058.4$, 42.2%; MTX group, adjusted $n = 1{,}026.9$, 43.2%). In both groups, the second most common cause of induction failure was the continuation of steroids in patients receiving concomitant steroid therapy or the initiation of steroids in patients not receiving concomitant steroid therapy (thiopurine group, adjusted $n = 820.1$, 32.7%; MTX group, adjusted $n = 769.4$, 32.4%). Induction failure in patients who were not receiving concomitant steroids was evaluated to exclude the effect of steroids on the induction of clinical remission. The incidence of induction failure in patients not receiving concomitant steroids was lower in the MTX group than in the thiopurine group (aOR = 0.740, 95% CI = 0.673–0.813, $p < 0.001$).

The median maintenance periods were 2.15 years [interquartile range (IQR) = 2.06–2.25 years] in the thiopurine group and 4.99 years (IQR = 3.52–6.60 years) in the MTX group. We used Kaplan–Meier curves to evaluate the difference in the risk of maintenance failure between the MTX and thiopurine groups. As shown in Supplemental Figure 2, the Kaplan–Meier curves overlapped; thus, the proportional hazard assumption was violated. Therefore, the time-dependent Cox proportional hazard model was used. There was no significant difference in the risk of maintenance failure within 1 year between the MTX and thiopurine groups [adjusted hazard ratio (aHR) = 0.991, 95% CI = 0.934–1.051, $p = 0.756$]. The risk of overall maintenance failure was higher in the MTX group than in the thiopurine group (aHR = 1.117, 95% CI = 1.047–1.191, $p = 0.001$).

Comparison of the risk of persistence failure between the thiopurine and MTX group

A total of 8,901 patients who continued thiopurine or MTX for at least 16 weeks were eligible for the analysis of persistence failure. The median persistence periods were 3.45 years (IQR = 1.61–6.18 years) in the thiopurine group and 1.46 years (IQR = 0.55–2.76 years) in the MTX group. The baseline characteristics of patients included in the analysis are shown in Supplemental Table 2. The covariate difference between the two groups was not significant (SMD < 0.2) except for sex and disease duration after the initiation of IMMs. Kaplan–Meier curves of cumulative incidence of persistence failure after 16 weeks from the index date indicated that the MTX group had a higher risk of persistence failure than the thiopurine group (log-rank, $p < 0.0001$; Supplemental Figure 3). The risk of persistence failure after 16 weeks from the index date was significantly higher in the MTX group than in the thiopurine group (within 1 year, aHR = 3.234, 95% CI = 2.829–3.698, $p < 0.001$; overall period, aHR = 2.888, 95% CI = 2.176–2.406, $p < 0.001$).

The risk of clinical failure according to IMM dose and MTX administration route

The risk of clinical failure according to IMM dose was analyzed, and the characteristics of patients treated with thiopurine and MTX according to IMM dose are shown in Supplemental Tables 3 and 4. In patients treated with thiopurines, the aOR for induction failure did not differ significantly according to thiopurine doses (aOR = 1.131, 95% CI = 0.953–1.338, $p = 0.156$). A Cox proportional hazard model showed that a hazard of maintenance failure within 1 year or the overall period was not related to the dose of thiopurine (maintenance failure within 1 year, aHR = 1.032, 95% CI = 0.889–1.338, $p = 0.677$; overall maintenance failure, aHR = 1.049, 95% CI = 0.944–1.167, $p = 0.374$). In patients treated with MTX, there was no significant effect of MTX dose on induction failure (aOR = 1.132, 95% CI = 0.965–1.327, $p = 0.128$). A Cox proportional hazard model revealed that the risk of maintenance failure was higher in the standard-dose MTX group than in the low-dose MTX group (maintenance failure within 1 year, aHR = 1.272, 95% CI = 1.104–1.466, $p = 0.001$; overall maintenance failure, aHR = 1.296, 95% CI = 1.134–1.480, $p < 0.001$).

Next, the risk of clinical failure according to the administration route of MTX was evaluated. The characteristics of patients treated with per oral (PO) or subcutaneous (SC)/intramuscular (IM) MTX are shown in Supplemental Table 5. SC/IM MTX administration was more likely to lead to induction failure than PO (aOR = 1.226, 95% CI = 1.024–1.466, $p = 0.026$). However, before adjusting for covariates with SMD ≥ 0.2, the result showed the opposite trend (aOR = 0.867, 95% CI = 0.750–1.001, $p = 0.053$). There was no significant difference in the risk of maintenance failure within 1 year or the overall period according to the administration route (failure within 1 year, aHR = 1.113, 95% CI = 0.960–1.291, $p = 0.155$; overall failure, aHR = 1.085, 95% CI = 0.945–1.247, $p = 0.248$).

Discussion

Our study revealed that among bio-naïve patients with CD, the MTX group had a higher risk of overall maintenance failure than the thiopurine group, although there was no difference in the failure risk within 1 year. The risk of persistence failure was also higher in the MTX group than in the thiopurine group. On the other hand, the risk of clinical failure did not differ between standard and low doses of thiopurines. Although there was no difference in induction failure according to MTX dose, standard doses of MTX were associated with a higher risk of maintenance failure than low doses. The risk of maintenance failure did not differ between SC/IV MTX administration and PO MTX administration. However, the results for induction failure according to the administration route of MTX could not be determined because of result inconsistency before and after adjusting for high SMD (≥ 0.2).

Regardless of concomitant steroids, induction failure was more common in the MTX group than in the thiopurine group. However, the risk of induction failure was higher in the thiopurine group than in the MTX group when only patients who did not receive concomitant steroids were analyzed. The reason why the thiopurine group did not show a consistent result in inducing CD remission may be that thiopurine takes a long response time rather than not affecting CD-related inflammation,[29] and concomitant steroid use is a more important factor in clinical induction than a type of IMM. Approximately 97% of the Korean population is obliged to enroll in the NHI program,[8] which requires previous medical records of clinical failure of IMM treatment for the coverage of biologics and small molecules. Because of the Korean NHI policy, Korean clinicians prefer to prescribe IMMs early in patients with moderate-to-severe CD, and Korean patients with CD were treated with thiopurines in the induction period in the real clinical setting.[30,31] Therefore, if used as a monotherapy, MTX may be a better choice than thiopurines for inducing clinical remission in bio-naïve patients with CD.

Our study demonstrated that the MTX group had a higher risk of clinical failure during the overall maintenance period, even though the specific causes of clinical failure were not available from the claim data. In addition, the MTX group exhibited a higher risk of persistence failure than the thiopurine group. A retrospective cohort study of patients with IBD, with an extended follow-up period (median follow-up duration >40 months), reported that discontinuation due to adverse effects was approximately twice as high for MTX than for thiopurine.[32] In addition, the difference in persistence failure between the MTX and thiopurine groups may be influenced

not only by adverse effects but also by treatment efficacy. A few studies showed no difference in treatment efficacy between MTX and thiopurine[33,34]; however, further studies are required because of small sample sizes and inconsistent definitions concerning remission.

Thiopurine-related leukopenia is frequently reported in Asian patients with CD because of a common missense variant of the nucleoside diphosphate-linked moiety X-type motif 15 (NUDT15) gene, which encodes R139C in Asians.[20,35] Approximately 25% and 2.5% of Asian populations are NUDT15 intermediate and poor metabolizers, respectively, whereas less than 1% of Western populations are NUDT15 intermediate and poor metabolizers.[14,36] Therefore, the frequent occurrence of NUDT15 mutations makes it difficult to increase thiopurine doses in Asian patients. In reality, the prescription doses of thiopurine in Asian patients were smaller than those in Western patients.[37] In the same vein, the number of patients with low doses of thiopurine was larger than that of patients with standard doses of thiopurine in our study. Meanwhile, some studies suggested that low doses of azathioprine ($<$1.5 mg/kg/day) are effective in managing CD in Asian patients.[38–40] The results of our study also support the notion that low doses of thiopurine treatment can have enough therapeutic effect in bio-naïve Asian patients with CD.

Our study showed that maintenance failure in the MTX group was associated with the dose-related adverse effects of MTX; however, there was no significant difference in induction failure according to MTX dose. Many patients with CD treated with MTX experience drug-related adverse effects, such as nausea and hepatotoxicity.[41] Although the ratio of patients who discontinue MTX due to adverse effects differs across related studies (6–50%),[42,43] cessation due to adverse effects is more common with standard rather than low doses of MTX.[44]

The difference in therapeutic effects according to the routes of MTX administration remains controversial. A previous study reported that parenteral MTX was more effective than PO MTX; however, the mean dose of parenteral MTX (24.6 mg/week) was higher than that of PO MTX (7.8 mg/week).[45] By contrast, other studies reported that the therapeutic effect of parenteral MTX was not superior to that of PO MTX.[6,46] In our study, the outcomes according to the route of MTX administration before and after adjusting for covariates with SMDs $\geqslant$0.2 were the opposite. Age at diagnosis, sex, and the ratio of patients who underwent bowel resection or concomitantly used steroids – which are factors related to the clinical course and prognosis of CD – differed highly according to the route of MTX administration.[47–49] Therefore, the reliability of findings regarding induction failure according to the MTX administration route is not high.

Our study has several strengths. First, this study compared the outcomes of thiopurine or MTX therapy in CD patients who were not exposed to either biologics or IMMs, whereas most previous studies evaluated the outcomes of MTX therapy in those who had failed thiopurine therapy.[5,6] Second, subgroup analyses were performed to compare the risk of clinical failure according to IMM administration doses or routes, which have not been well studied. Finally, the study design and applied methods were robust. From the beginning, the study was designed in collaboration with a professional statistician who also performed all statistical analyses.

However, this study has several limitations. First, clinical response is most widely assessed based on clinical evaluations, such as the Crohn's Disease Activity Index (CDAI) and Harvey–Bradshaw Index (HBI). The CDAI and HBI include factors such as stool frequency, abdominal pain, and general well-being, which the claims databases cannot cover. As our study defined clinical failure using newly imposed operation codes or changes in medication codes, there may be a gap in the definition of clinical failure between real clinical settings and our study. However, medical events such as medication changes or operations are more objective criteria for assessing clinical failure than CDAI and HBI. Second, the number of patients in the thiopurine group was much greater than that in the MTX group, and many clinical variables differed between the thiopurine and MTX groups. However, the wide discrepancy in the proportions of MTX- and thiopurine-treated patients is a common limitation in studies comparing the efficacy of thiopurine and MTX.[50,51] IPTW was used to reduce the influence of possible selection bias and potential confounding factors. Third, because information regarding the weight of individual pediatric patients was not

available from the claims database, the IMM doses for pediatric patients were determined based on the average body weight by age. Large-scale, well-designed, prospective studies that compare the treatment efficacy of thiopurine and MTX are required to overcome the limitations of this study.

In conclusion, our study enriches the knowledge regarding the treatment efficacy of thiopurines and MTX for bio-naïve patients with CD. Patients treated with MTX had a higher risk of maintenance failure than those treated with thiopurines. Treatment efficacy did not differ according to thiopurine dose; however, standard doses of MTX showed a higher probability of maintenance failure compared to low doses of MTX. Our findings may help clinicians develop appropriate treatment plans for bio-naïve patients with CD.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of the Seoul National University Bundang Hospital (IRB No. X-2202-741-902). This manuscript is original and has not been published before. The manuscript has been read and approved by all named authors.

Consent for publication

Not applicable.

Author contributions

Yu Kyung Jun: Conceptualization; Data curation; Funding acquisition; Writing – original draft; Writing – review & editing.

Eunjeong Ji: Conceptualization; Data curation; Formal analysis; Methodology; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Supplemental material

Supplemental material for this article is available online.

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